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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/772,538	01/29/2001	Cornelius Frommel	ABOHM1.001CP1	9231

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KNOBBE MARTENS OLSON & BEAR LLP
2040 MAIN STREET
FOURTEENTH FLOOR
IRVINE, CA 92614

EXAMINER	
BORIN, MICHAEL L	

ART UNIT	PAPER NUMBER
1631	

DATE MAILED: 11/02/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/772,538	FROMMEL ET AL.	
	Examiner	Art Unit	
	Michael Borin	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12 and 14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12 and 14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Detailed Action

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 05/21/2004 has been entered.

Priority

2. Acknowledgment is made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d). The English translation of priority document, DE 31758.1 filed 07/15/1998 has been received from applicant and entered 05/21/2004.

Consequently, the rejection under 35 U.S.C. 102(b) over Preisner et al. (J. Mol. Biol., 1998, 280, 535-550) is withdrawn.

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 1-12, 14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject

matter which applicant regards as the invention. The rejection is applied for the following reasons:

A. Claim 1(a). The term "secondary structural elements" is a relative term which renders the claim indefinite. The term is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The dictionary definition of "secondary structure" is, for example,

> The folded, coiled or twisted shape a polypeptide or polynucleotide chain takes on when hydrogen bonds form between adjacent parts of the molecule.

See http://biotech.icmb.utexas.edu/search/dict-search.phtml?title=secondary+structure

It is not clear what constitutes "elements" of the secondary structure. Are they the size of atoms, molecules, protein folds, etc?

Further, in regard to claim 1(a) it is directed to determining "elements" of the secondary structure that "constitute the ligand-binding site". The specification provides support for the claimed method in general, but nowhere does the instant specification disclose specific method steps required for determination of the ligand-binding site and its elements.

B. Claim 1(b). It is not clear what is the difference between "secondary structural elements" of claim 1(a) and "molecular surface elements" of claim 1(b). According to specification (p. 4, top)

> The molecular surface element is representative of the target protein to which the ligand has been determined to bind and is built up by secondary structural elements derived from the target protein.

Does it mean that "molecular surface elements" are comprised of "secondary structural elements" (e.g., are comprised of alpha-helices)? Then, the "secondary structural elements", which are smaller in size, has already been determined in step 1(a) and it is not clear what is the difference between method steps 1(a) and 1(b). Contrary, the language of claim 2 and other parts of specification (e.g., p. 6, lines 18-20) indicates that molecular surface elements are a part of external surfaces of "secondary elements". Please clarify.

C. Claim 1(c). The term "molecular surface patches" is not clear and is a relative term which renders the claim indefinite. It is understood that the "patch" is a certain known template secondary protein surface (structure), for example stored in a database. However, the term is not defined by the claim; the specification, although describing particular example of "Dictionary of Interfaces in Proteins", does not provide a standard for ascertaining the requisite structure/size of a "patch", and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

D. Claim 1(d). The term "effecting coordinate transformation" is not clear. The specification does not disclose the meaning of "coordinate transformation" and

specific method steps involved in "effecting" it. The disclosure, for example, states, p. 5, lines 10-15:

> "Co-ordinate transformation is effected on the basis patches found together with the corresponding contact patches on molecular stzrface elements that are desned in a) and b) with an rms value of less than 2A. In particular a coordinate transformation is done to transform the surface found into the search area for given proteins."

or in the description of the example, p. 9, line 21:

> After coordinate transformation, the basis patches found lie on the atoms of the binding sites, with the counterparts (contact patches) in the binding pocket.

In both instances, it is not clear how "coordinate transformation" is being "effected".

E. Claim 1(d). It is not clear from the claim language how this method step is related to other steps of the method. Neither of the subsequent steps (e) or (f) rely on the results of step (d).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject

matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

4. Claims 1-12, 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lesk et al. (Acta Crystallographica, Section A: Foundations of Crystallography (1986), A42(2), 83-5) or Connoly et al (Biopolymers, vol. 25,1229-1247, 1986) or Peters et al (Journal of Molecular Biology, (1996 Feb 16) 256 (1) 201-13) in view of Godden et al (Journal of Molecular Graphics & Modelling (1998), 16(3), 139-143).

The instant claims are drawn to method for identifying compounds as potential ligands for a protein having a ligand-binding site, comprising:

a) determining secondary structural elements of the protein that constitute the ligand-binding site;

b) breaking down the molecular surface of the ligand-binding site of the protein into molecular surface elements;

c) identifying known molecular surface patches that are complementary to a neighboring molecular surface element;

(d) effecting coordinate transformation of the molecular surface patches identified in step c) with a neighboring molecular surface element, based on a starting element at an rms value less than 2A;

(e) identifying counterparts of the molecular surface patches in known compounds; and

(f) assessing the fit of the compounds identified in step (e) in terms of local packing density, wherein a better fit indicates a better potential for the compounds to be ligands of the protein.

To the extent the claim language ambiguity (see rejections under the second paragraph of 35 U.S.C. 112) allows, the method is understood as follows: first, a "molecular surface element" that represents a part of a ligand-binding site of a protein and is built up by "secondary structure elements" is identified; then, a database is searched to identify a matching molecular surface ("molecular surface patch") which is complementary to the surface of the "molecular surface element"; alignment of the "molecular surface patch" and "molecular surface element" is verified by correlation of their coordinates; thereafter, similar compounds having such "patches" are identified and their ability to serve as a ligand is verified by estimation of local packing density on the surface of the protein.

The concept of matching corresponding receptors and ligands by their shape complementarity is well known in biochemistry. Thus, in their early work, Lesk et al teach the importance of surface complementarity and describe a method whereby stereochemical set of peaks representing ligand binding site (i.e., "molecular surface element") is determined, matched with a known small molecule analog (which represent "molecular surface patch"). Although the reference does not teach specifically identification of other counterparts of the known analog, it suggests that other ligands similar in nature to the known analog can be searched in databank of known drugs.

Connoly et al. teach several ways to measure the shape of protein surface regions and describe docking algorithm to match hemoglobin dimers. The coordinates of a second protein, a potential ligand, are transformed on the first protein so that the rms value of the coordinate points of the two surfaces is less than 1.0 A (see p. 1237, paragraphs two to four.) If the transformation of the coordinates is successful, that is, if the atoms of the first and second protein are less than 2A apart, the molecular surface located in the interface is calculated. The docking then corresponds to a the predicted manner of association of the two molecules (p. 1239, first paragraph). The reference does not teach using secondary structure elements to identify corresponding surface elements in interacting compounds; however, it considers interaction surface in terms of geometrical parameters which brings to the same shape matching result. The

reference does not teach specifically identification of other counterparts of the known analog.

Norel et al teach that, geometrically, acceptable receptor-ligand interaction requires close contact between corresponding patches of surfaces of the receptor and of the ligand. The reference describes method of identifying docking of ligand to receptor by scanning groups of surface dots (or atoms) of receptor and a potential ligand and detecting optimally matched surfaces. This reads on identifying "molecular surface patches" of ligand that are complementary to the surface of the "molecular surface element" of receptor. The reference does not teach that identified "patches" can be then used for search of other potential ligands.

Peters et al (Journal of Molecular Biology, (1996 Feb 16) 256 (1) 201-13) teach that specific binding sites are located on the surface of proteins and are determined by geometrical arrangements of molecules. The reference describes method of identifying ligand binding sites which analyzes shapes of protein surface and finds cavities on the surface of the protein (i.e., surface patches) responsible for ligand binding. The study teaches that small ligands bind at pockets in the surface, whereas protein-protein interactions occur between flat areas of protein surface. Peters does not teach identifying potential ligands by coordinate

transformation with a known patch and assessing fit of a potential ligand in terms of local packing density.

If there are any differences between Applicant's claimed methods and that of the prior art, the differences would be appear minor in nature. It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to that surface of a known compound (or patch) can be used for database searching of new potential ligands. See, for example, Godden et al who describe identification of potential ligands based on scoring of their surface complementarity and showed that contact scoring works well to find new potential ligands. Further, it would be obvious to evaluate fit of a potential ligand and receptor as in step (f) of the claimed method, as it would facilitate determination of a successful ligand-receptor binding.

5. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Borin whose telephone number is (571) 272-0713. The examiner can normally be reached on 9am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward can be reached on (571) 272-0722.

The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Michael Borin, Ph.D.
Primary Examiner
Art Unit 1631

mlb